

Title : REPRODUCTIVE SAFETY OF ENFLURANE IN FEMALE MICE

Authors : R. S. Wharton, M.D., and R. I. Mazze, M.D.

Affiliation: Department of Anesthesia, Stanford University School of Medicine, Stanford, CA 94305, and Anesthesiology Service, Veterans Administration Medical Center, Palo Alto, CA 94304

Introduction. Rates of infertility and spontaneous abortion have been reported to be increased among female operating room personnel.¹ Occupational exposure to trace concentrations of waste anesthetic gases has been suggested, but not established, as the cause of these increases. The reproductive toxicity of chronic subanesthetic exposure has previously been assessed for halothane.² The present study examines the effect of chronic enflurane exposure on mating behavior, fertility and reproductive wastage in female Swiss/ICR mice.

Methods. Two hundred-sixteen female and 108 male 9-week-old virgin Swiss/ICR mice were randomly divided into five groups. Group 1 mice (colony control) were untreated; females in group 2 (treatment control) were exposed to compressed air for four hours daily in an inhalation chamber. Females in groups 3 through 5 were treated four hours daily, 7 days/week with enflurane 0.01%, 0.1% and 1.0%, respectively; after the 21st day of treatment, the high dose was changed to 0.5% because of significantly decreased weight gain in that group. Males in all groups were untreated. Following 21 days of treatment, females were recaged in pairs and one male was placed with each pair of females nightly for seven nights. Each morning, females were inspected for vaginal copulatory plugs. Females that did not show copulatory plugs after seven nights were mated with a new male for seven additional nights. Daily exposures of females were continued during mating and through day 17 of pregnancy. On day 18 of pregnancy, each female was killed by cervical dislocation and the uterus was examined for the number and location of implantations, live and dead fetuses, and resorptions (equivalent to abortions in humans). The length, weight and sex of each live fetus were determined. Data were analyzed by one-way analysis of variance and the Student-Neuman-Keuls *a posteriori* contrast test; $p < 0.05$ was considered significant.

Results. Copulation and pregnancy rates were the same in all groups (Table). The mean number of implantations per dam was greater in the colony control than in the treatment control group; however, there were no differences between the enflurane exposed and the treatment control groups. There were no differences among the five groups in the number of live fetuses/dam, percentage of resorptions or fetuses dead in utero, mean fetal weight, or sex ratio of live fetuses.

Discussion. In the present study, enflurane exposure did not adversely affect re-

production. These results differ from those of a previous study of halothane: daily four-hour exposure to 0.3% resulted in decreased pregnancy and implantation rates.² Although the two studies were not identically designed, the results suggest that toxic thresholds for these agents differ, enflurane being less toxic. Furthermore, the highest enflurane concentration to which pregnant mice were exposed, 0.5%, is 100 to 500 times greater than the concentration in unscavenged operating rooms. It therefore appears that enflurane provides a large margin of safety with respect to the potential reproductive toxicity resulting from occupational exposure.

References.

1. ASA Ad Hoc Committee: Occupational disease among operating room personnel. *Anesthesiology* 41:321-340, 1974
2. Wharton RS, Mazze RI, Baden JM, et al: Fertility, reproduction and postnatal survival in mice chronically exposed to halothane. *Anesthesiology* 48:167-174, 1978
3. Lecky JH: Anesthetic trace levels in U.S. hospitals (Abstr). American Society of Anesthesiologists Ann. Meeting, 1975, pp 291-292 (Supported by NIH Grant GM 25952)

Table. Summary of Results

Group	1	2	3	4	5
	Controls		Enflurane, %		
Exposure	Colony	Treat- ment	0.01	0.1	1.0/ 0.5*
No. of females	48	48	40	40	39
Copulation rate(%)	89.6	85.4	90.0	95.0	94.9
Pregnancy rate(%)	89.6	91.7	92.5	100.0	94.9
Implants/dam**	13.63 +0.46 ⁺	12.22 +0.42	13.24 +0.28	11.97 +0.30	12.03 +0.39
Live fetuses/dam**	12.22 +0.44	11.22 +0.41	12.06 +0.28	10.86 +0.32	10.89 +0.44
Resorbed(%)**	9.66 +1.35	7.74 +1.67	8.70 +1.41	8.31 +1.42	9.74 +1.93
Dead in utero(%)**	0.19 +0.19	0.42 +0.29	0.0 +0.0	1.02 +0.61	0.42 +0.42
Mean fetal weight(g)**	1.31 +0.01	1.34 +0.02	1.33 +0.02	1.33 +0.01	1.28 +0.02

* 1.0% prior to mating; 0.5% thru pregnancy

** Mean + S.E.

⁺ $p < 0.05$ vs. Treatment control